NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional procedure consultation document

Irreversible electroporation for treating pancreatic cancer

Irreversible electroporation is a procedure used to treat pancreatic cancer. Special needles are inserted through the skin into the tumour in the pancreas. Short electrical pulses of a high voltage current are then used to kill the cancer cells.

The National Institute for Health and Care Excellence (NICE) is examining irreversible electroporation for treating pancreatic cancer and will publish guidance on its safety and efficacy to the NHS. NICE's interventional procedures advisory committee has considered the available evidence and the views of specialist advisers, who are consultants with knowledge of the procedure. The advisory committee has made draft recommendations about irreversible electroporation for treating pancreatic cancer.

This document summarises the procedure and sets out the draft recommendations made by the advisory committee. It has been prepared for public consultation. The advisory committee particularly welcomes:

- comments on the draft recommendations
- the identification of factual inaccuracies
- additional relevant evidence, with bibliographic references where possible.

Note that this document is not NICE's formal guidance on this procedure. The recommendations are provisional and may change after consultation.

The process that NICE will follow after the consultation period ends is as follows.

- The advisory committee will meet again to consider the original evidence and its draft recommendations in the light of the comments received during consultation.
- The advisory committee will then prepare draft guidance which will be the basis for NICE's guidance on the use of the procedure in the NHS.

For further details, see the Interventional Procedures Programme process guide, which is available from the NICE website.

Through its guidance NICE is committed to promoting race and disability equality, equality between men and women, and to eliminating all forms of discrimination. One of the ways we do this is by trying to involve as wide a range of people and interest groups as possible in the development of our interventional procedures guidance. In particular, we aim to encourage people and organisations from groups who might not normally comment on our guidance to do so.

In order to help us promote equality through our guidance, we should be grateful if you would consider the following question:

Are there any issues that require special attention in light of NICE's duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations between people with a characteristic protected by the equalities legislation and others?

Please note that NICE reserves the right to summarise and edit comments received during consultations or not to publish them at all where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would otherwise be inappropriate.

Closing date for comments: 18 November 2016

Target date for publication of guidance: February 2017

1 Draft recommendations

1.1 Current evidence on the safety and efficacy of irreversible electroporation for treating pancreatic cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.

1.2 Further research, preferably in the form of randomised controlled trials, should assess the effect of the procedure on local tumour control, patient survival, pain control and quality of life.

2 Indications and current treatments

2.1 Pancreatic cancer usually causes few symptoms until the disease has reached an advanced stage, so most cases are diagnosed when curative treatment is not possible.

2.2 Because potentially curative surgery is seldom an option, most patients can only be offered palliative treatment to relieve their symptoms. Stenting of the bile duct and duodenum can be used to relieve obstruction caused by pancreatic cancer, and sometimes surgical bypass is needed. Other treatment options include palliative chemotherapy and radiotherapy.

3 The procedure

3.1 The aim of irreversible electroporation (IRE) is to destroy cancerous cells by subjecting them to a series of short electrical pulses using high-voltage direct current. This creates multiple holes in the cell membrane, irreversibly damaging the cells' homeostatic mechanisms and leading to cell death.

3.2 In pancreatic cancer, IRE is usually done with the intention of prolonging survival in people with locally advanced disease, or to treat resection margins to increase the success of curative surgical resection.

3.3 The procedure is done with the patient under general anaesthesia. A neuromuscular blocking agent is essential to prevent uncontrolled severe muscle contractions caused by the electric current. Several electrode needles (typically 3–5) are introduced percutaneously (or by open surgical or laparoscopic approaches), and inserted in and adjacent to the tumour using image guidance. A series of very short electrical pulses is delivered over several

minutes to ablate the tumour. The electrodes may be repositioned under imaging guidance to extend the zone of electroporation until the entire tumour and an appropriate margin have been ablated.

3.4 To minimise the risk of arrhythmia, cardiac synchronisation is used to time delivery of the electrical pulse within the refractory period of the heart cycle.

4 Efficacy

This section describes efficacy outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

4.1 In a systematic review of 74 patients (from 4 studies) with locally advanced pancreatic cancer (LAPC) treated by irreversible electroporation (IRE), at 6 months, overall survival (OS) was 40% in 1 study (n=5) and 70% in another (n=14). In another study in the same review, there was a statistically significant survival benefit with IRE plus chemotherapy or radiotherapy (n=54) compared with chemotherapy or radiotherapy alone (n=85; local progression-free survival [PFS] 14.0 months versus 6.0 months, p=0.01; distant PFS 15.0 months versus 9.0 months, p=0.02; overall survival [OS] 20.2 months versus 11.0 months, p=0.03). Patients who had resection with simultaneous IRE (19/54) did not have significantly improved survival compared with IRE alone (35/54; 23.1 months versus 17.2 months, p=0.1). In a case series of 200 patients with locally advanced (stage III) pancreatic adenocarcinoma treated by IRE (n=50 for IRE plus resection for margin enhancement and n=150 for IRE alone), the median OS from date of diagnosis was 28.3 months (range 9.2–85.0 months) for the resection plus IRE

group (n=50) and 23.2 months (range 4.9–76.1 months) for the IRE alone group (n=150). The median OS from the day of IRE treatment for the resection plus IRE group was 23.0 months (range 8.3–36.3 months) and for IRE alone group was 18.0 months (range 4.9–55.4 months). The median overall PFS for all patients was 12.4 months and distant PFS was 16.8 months.

4.2 In the case series of 200 patients with LAPC (stage III) treated by IRE plus resection for margin enhancement (n=50) or IRE alone (n=150), recurrence (defined as persistent viable tumour assessed using dynamic imaging and compared with pre-IRE scanning or tissue diagnosis) was reported in 29% (58/200) of patients at a median follow-up of 29 months. The most common site of disease recurrence was the liver (n=34), followed by lymph nodes (n=11) and the peritoneum (n=7). Local recurrence after IRE success (defined as development of new low density lesions of 1 cm in the IRE region even in the absence of symptoms) was reported in 6 patients. In a case series of 50 patients with LAPC (T4 lesions) treated by IRE for primary treatment (n=29) or margin extension (n=24), overall recurrence was 58% after a median follow-up of 8.69 months (range 0.26–16.26 months). Distant recurrence was 47% at a median of 9.20 months (95% confidence interval [CI] 6.66 to 16.98) and local recurrence was 11% at a median of 8.60 months (95% CI 5.51 to not reached). Neither local nor distant recurrence differed statistically significantly between the primary treatment group (p=0.500, log rank) and the margin-extension group (p=0.361, log-rank).

4.3 In a case series of 65 patients with LAPC treated by IRE, the median disease-free survival was statistically significantly less in patients who had local disease recurrence (n=17) than in patients

with no recurrence (n=48); 5.5 months compared with 12.6 months, p=0.03).

4.4 In a case series of 21 patients with unresectable LAPC (TNM stage III) treated by IRE, quality of life was measured at each clinical follow-up using the Karnofsky performance scale (range 0% to 100%, with 100 representing 'completely normal' life). Quality of life declined slowly in both groups until about 8 weeks before death (when there was a sharp decline). Performance status was 70% or over in 81% of patients in the IRE group (n=21) compared with 74% in a matched cohort (n=32) (p=0.076).

4.5 The specialist advisers listed key efficacy outcomes as overall and relapse-free patient survival, local tumour control, and tumour response (complete or partial).

5 Safety

This section describes safety outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

5.1 In a systematic review of innovative ablative therapies for locally advanced pancreatic cancer (LAPC) including 141 patients (from 4 studies) treated by irreversible electroporation (IRE), overall mortality rate was 3% (3/92) in 3 studies using IRE. Two of these deaths were in patients treated by an open approach and 1 was in a patient treated by a percutaneous approach. The IRE-related mortality rate was 2% (2/87), and was in patients treated by an open approach. Death within 90 days (median 26 days, range 8–42 days) after an IRE procedure was reported in 11% (6/50) of patients in a case series of 50 patients with LAPC (T4 lesions)

treated by IRE for primary treatment (n=29) or margin extension (n=24). Five of these deaths were in the primary treatment group (n=29) and 1 was in the margin-extension group (n=24).

5.2 In the systematic review of 141 patients, 48% (44/92) of patients reported complications. Of these, 51% (41/81) were in patients treated by an open approach and 27% (3/11) were in patients treated by a percutaneous approach. In all, 13% (5/38) of complications were related to an IRE procedure (open 15% [4/27]; percutaneous 9% [1/11]). Morbidity related to IRE mainly consisted of duodenal leakage (in patients with transduodenal needle placement or stent removal), pancreatic leakage, bile leakage and progression of portal vein thrombosis.

5.3 Pancreatic complications (including pancreatic leakage, pancreatitis and pancreatic failure) were reported in 4% (2/50) of patients in the IRE plus resection group (n=50) and none in the IRE alone group (n=150) at 90-day follow-up in a case series of 200 patients with stage 3 LAPC treated by IRE. Pancreatic fistula (treated with a stoma bag and antibiotics) in 1 patient and peripancreatic abscess (treated with percutaneous drainage and antibiotics) in 1 patient were reported in a case series of 21 patients with unresectable pancreatic cancer treated by IRE.

5.4 Liver complications (including ascites, biliary stricture, liver dysfunction and failure) were reported in 14% (7/50) of patients in the IRE plus resection group (n=50) and 9% (13/150) of patients in the IRE alone group (n=150) at 90-day follow-up in the case series of 200 patients. Biliary peritonitis, cholangitis and liver abscess (needing revision surgery and antibiotics) were reported in 1 patient in the case series of 21 patients. Duodenal and bile duct necrosis (needing transhepatic drain insertion) and haemorrhage (needing

transfusion) were reported in 1 patient in the case series of 50 patients. Bile duct obstruction and biliary stent obstruction after IRE treatment were reported as the most common reasons for readmission in another case series (conference abstract) of 50 patients with LAPC treated by IRE. Bile leakage was reported in 3 patients in a case series of 48 patients with borderline resectable PC or LAPC treated by IRE. Liver insufficiency was reported in 4 patients in a case series of 65 patients with LAPC treated by IRE.

5.5 Severe complications including bowel perforation (abscess formation and perforation of the duodenum and transverse colon close to the stent) and bleeding from a pancreatic branch of the superior mesenteric artery (due to pseudo-aneurysm) leading to death were reported after IRE treatment in a case report of 1 patient with pancreatic cancer who had a metallic stent in the common bile duct. Duodenal leakage (from transduodenal IRE needle placement) was reported in 1 patient in 1 study included in a systematic review of 74 patients with LAPC treated by IRE. Fistula and abscess in the abdominal wall (treated with drainage and antibiotics) was reported in 1 patient in the case series of 21 patients. Delayed gastric emptying (needing total parenteral nutrition and percutaneous endoscopic gastrostomy tube insertion) in 4 patients, upper gastrointestinal bleeding (needing transfusion and medical management) in 3 patients, duodenal cutaneous fistula in 1 patient and perforated gastric ulcer (needing drain placement) in 1 patient were reported in the case series of 50 patients. Ileus was reported in 5 patients in the case series of 65 patients treated with IRE. Small bowel leakage (grade 2) was reported in 1 patient in the case series of 48 patients. Other gastrointestinal complications (including anorexia, dehydration, gastritis, heartburn, nausea, vomiting) were reported in 16% (8/50)

patients in the IRE plus resection group (n=50) and 25% (38/150) patients in the IRE alone group (n=150) at 90-day follow-up in the case series of 200 patients.

5.6 Vascular complications (including deep vein thrombosis, pseudo-aneurysm, hepatic arterial thrombosis, non-occlusive superior mesenteric vein/portal vein thrombosis) were reported in 8% (4/50) of patients in the IRE plus resection group (n=50) and 5% (7/150) of patients in the IRE alone group (n=150) at 90–day follow-up in the case series of 200 patients. Intraoperative haemorrhage (needing transfusion) and angiogram embolisation of the gastroduodenal artery leading to multiorgan failure was reported in 1 patient in the case series of 50 patients. Disseminated intravascular coagulopathy (leading to death 7 days after IRE because of intracranial haemorrhage) was reported in 1 patient in a case series of 8 patients with borderline resectable PC or LAPC treated by IRE. Hepatic artery graft failure was reported in 1 patient in the case series of 48 patients. Partial splenic infarction (needing no treatment) in 1 patient was reported during percutaneous IRE ablation in a case series of 15 patients with LAPC or metastatic disease treated by IRE.

5.7 Cardiovascular complications (including atrial fibrillation) were reported in 4% (2/50) of patients in the IRE plus resection group (n=50) at 90–day follow-up in the case series of 200 patients. Arrhythmia developed in 2 patients during IRE procedures in the case series of 8 patients.

5.8 Pneumothorax (n=1) and pulmonary problems (n=3) were reported in the studies included in the systematic review of 74 patients

5.9 Sepsis needing reoperation was reported in 1 patient in the case series (conference abstract) of 50 patients treated by IRE. The patient died postoperatively. Infection was reported in 6% (3/50) of patients in the IRE plus resection group (n=50) and 9% (13/150) of patients in the IRE alone group (n=150) at 90-day follow-up in the case series of 200 patients. Deep surgical site infection (needing drain placement) was reported in 3 patients in the case series of 50 patients treated by IRE.

5.10 The case series of 200 patients also reported other complications such as urinary tract problems (in 7 patients), renal failure (in 1), wound problems (in 6), neurological changes (in 4), haematological events (in 2) and other adverse events (in 23). The case series of 48 patients also reported complications such as hepatojejunostomy stricture (in 1 patient), pain (in 1) and postoperative bleeding (in 2).

5.11 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers listed the following anecdotal adverse events: vessel occlusion (permanent or transient and due to oedema post IRE causing compression of an involved superior mesenteric vein). They considered that the following were theoretical adverse events: damage to major arteries or veins, gastro-intestinal tract injury (for example, stomach, duodenum, small or large bowel).

6 Committee comments

6.1 The committee noted that most of the evidence was from open or laparoscopic irreversible electroporation procedures. The

committee was informed that there is increasing use of the percutaneous approach.

7 Further information

7.1 For related NICE guidance, see the NICE website.

7.2 Patient commentary was sought but none was received.

7.3 This guidance is a review of NICE's interventional procedure guidance on irreversible electroporation for treating pancreatic cancer: http://www.nice.org.uk/IPG442

Tom Clutton-Brock
Chairman, interventional procedures advisory committee
October 2016